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The Formation and Properties of Diphenyl Sulphide and Some of Its Derivatives

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Chem.

The Formation and Properties of Diphenyl Sulphide and Some of its Derivatives

By

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Andrew C. Lovett

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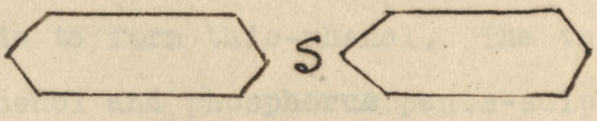
INTRODUCTION

The relationship between oxygen and sulphur, indicated by their positions in the periodic classification of the elements, is supported by a study of their carbon derivatives. There is a well-known group of sulphur compounds analogous to the monohydric phenols. These are known as thio-phenols. Similarly, a group corresponding with the aromatic ethers is known as the thio-ethers, or aromatic sulphides. Several of the aromatic sulphides and their derivatives are known. Diphenyl sulphide, the subject of this investigation, is probably the best known.

Diphenyl sulphide may be considered as the sulphide of benzene. The structure of the compound is given below:



I

Diphenyl sulphide is a colorless liquid with an odour similar to that of leeks. It has a boiling point of 292°C, and its specific gravity is 1.12[1].

The compound may be prepared by any of the following methods:

(1) By distilling phenol with phosphorus penta-sulphide and thio-phenol;

(2) By treating sodium benzol sulphonate with phosphorous pentasulphide;

(3) By heating mercury-diphenyl with sulphur;[2]

(4) By heating sulphur with diphenyl sulphone in the presence of an oxidant;[3]

(5) By the action of finely powdered sulphur and aluminum chloride, or sulphur hypo-chloride upon benzene;[4]

(6) Diphenyl sulphide and its homologues are readily prepared by heating aromatic lead mercaptides with halogen benzols;[6]

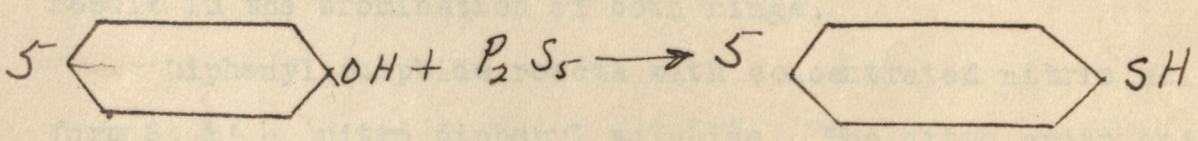
(7) By heating sodium mercaptides with iodo-benzol in the presence of powdered copper;[6] and

(8) By the action of thio-phenol on phenyl diazonium chloride.

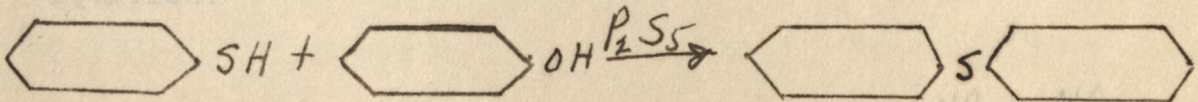
Method (1) gave the best results of the three methods attempted. The other methods used were (4) and (5). The percentage yield in the first case was 74.26. The percentage yield in (4) was 32.7. The percentage yield in case (5) was 21.3.

In case (1) phenol is allowed to react with phosphorus penta-sulphide to form thio-phenol. The thio-phenol is then mixed with phenol and phosphorus penta-sulphide, forming diphenyl sulphide.

Equation:



II



Apparently, when thio-phenol, phenol and phosphorus penta-sulphide are mixed, the phosphorus penta-sulphide plays the role of a catalyst, for the simple reason that thio-phenol and phenol alone will react to form diphenyl sulphide, but the process is

relatively slow.

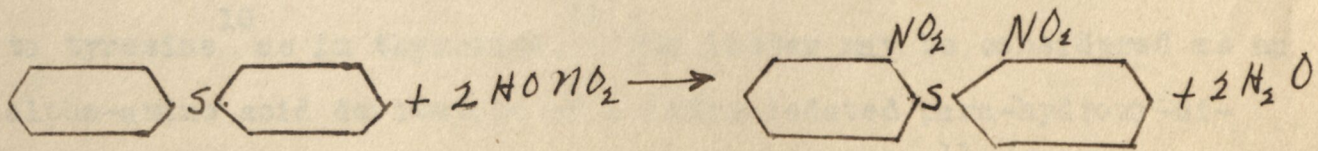
In order to obtain the best results, care should be exercised to see that the temperature, during the process of refluxing does not rise above 250°C. If the temperature is allowed to rise above 250°C, a relatively large quantity of the disulphide compound will be formed. It is better to carry the experiment on at a temperature of 250°C over a period of several hours rather than carry it on at a higher temperature over a shorter period of time. If this precaution is not taken, a large quantity of the disulphide compound will be formed along with a black resinous residue. The quantity of the resinous material varies directly with the temperature of the system.

As in the case of benzene, bromination and nitration take place readily. Oxidation of the side chain to form acids is not a difficult procedure.

Bromination takes place easily with the aid of a carrier. Iron will serve the purpose well. It is not practical to brominate one of the rings. Any attempt to brominate one of the rings will result in the bromination of both rings.

Diphenyl sulphide reacts with concentrated nitric acid to form 2, 2' - nitro diphenyl sulphide. The nitro group enters each ring of the compound with the formation of water.

Equation:



III

Dehydrating agents may be used to a decided advantage

to take up the water that is formed, which, if allowed to remain in the system as such, will dilute the nitric acid and prevent the reaction. Concentrated sulphuric acid, or glacial acetic acid are the best dehydrating agents for this purpose. Glacial acetic acid has preference over concentrated sulphuric acid because it has been observed that a much smaller quantity of the tarry residue is formed when the former is used. Another important consideration in connection with nitration is not to allow the temperature to rise above 45 to 50°C, as well as the use of a calculated quantity of the nitrating mixture; the latter factor being of primary importance.

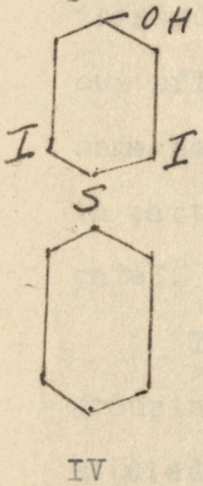
Hilbert and Johnson[7] extended their research program on germicides into the field of the diaryl-sulphide phenols. Para-Hydroxy diphenyl-sulphide, with its high germicidal value and low toxicity(phenol coefficient 115)has proved the most promising of the derivatives thus far examined.

It has been well proved that the substitution of halogen in the benzene ring nucleus of phenolic compounds leads to derivatives of considerably higher germicidal power than is possessed by the unsubstituted compounds.[8]

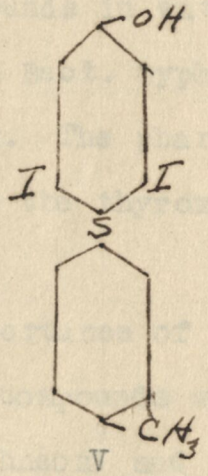
Bass and Johnson[9] have studied the antiseptic power of some iodine derivatives of diphenyl-sulphide phenols. It was observed that this element functions in a manner important to animal metabolism when present in compounds structurally related to tyrosine[10] as in thyroxine.[11] The latter may be considered as an alpha-amino acid derivative of a tetra-iodated para-hydroxy-diphenyl oxide. The results obtained by Harington[11] lend new light to the postulation that iodated derivatives of the structually related para-hydroxydiphenyl sulphide may also possess thyroxine-

like activity, or exercise some other specific physiological action of therapeutic value.

Two isomers di-iodo-diphenyl sulphide phenols(IV) and (VI) and their respective methyl homologs(V) and (VII)have been synthesized. In order to obtain an indication of the possible effectof substituting a halogen in the second benzene ring[12], the compound (VIII)was prepared. No attention, however, was paid to thyroxine-like constructions in which the iodine atoms occupied the meta positions with respect to the hydroxyl group, or unsymmetrical positions in the benzene rings. The spacial influence of iodine to the hydroxyl group in sulphide phenols upon the antiseptic power of such combinations has not been well worked out.



IV



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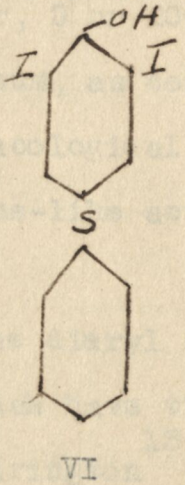
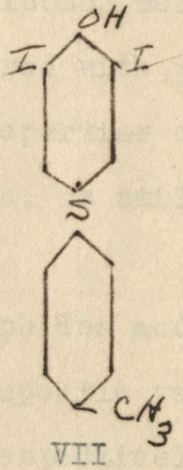
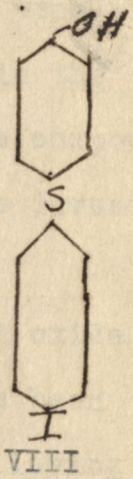


VI

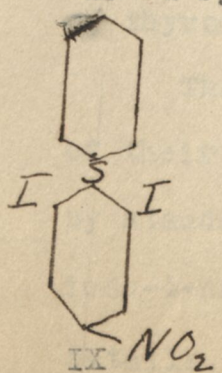


VII

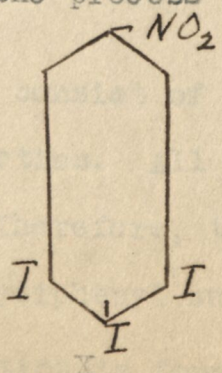


VIII

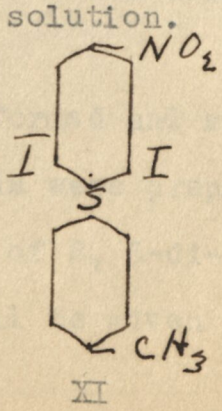
In order to obtain the intermediates desired for the final synthesis of phenols IV and V, 3, 4, 5-tri-iodonitrobenzene, X, was condensed with sodium thiophenate and sodium para-cresolate, respectively. It was observed that the best results were obtained by carrying on the process in 90% alcohol solution.



IX



X



XI

The nitro compounds IX and XI were reduced with stannous chloride and hydrochloric acid to the corresponding amines. It was observed that the iodine atoms substituted in the ring were not replaced. The amines formed were weakly basic, and were prepared by passing anhydrous hydrogen chloride into absolute ether solutions of the amines. They were successfully diazotized by suspending the hydrochloride in glacial acetic acid and treating it with butyl nitrite.

Bass and Johnson[9] observed that the extreme solubility of their iodated phenols prevented them from exhibiting any pronounced bactericidal properties. Saturated solutions of all five iodated compounds in water, 5 or 20% alcohol solution, were without effect on Bact. typhosum, as compared with phenol in the same solvents. The pharmacological properties of these compounds in particular the thyroxine-like action, is still to be investigated.

The importance of the diaryl sulphides and diaryl oxide groupings in compounds which have therapeutic value has been studied by Johnson[7] and Harington[13], respectively. Believing that some similarity should exist between the diaryl sulphides and the sulphur ether analogs, Sandin and Drake[14] prepared and studied both groups.

The objectives of Sandin and Drake were to synthesize a sulphuric analog of thyroxine[15] and also two oxygen ether isomers of thyroxine.

The tables below consist of the compounds formed and some of their general properties. All of the compounds were prepared by standard methods. Therefore, the preparation of 2, 6-diiodo-4-nitro-4'-methoxydiphenyl sulphide only will be given in details. This preparation is found on Page 13.

DERIVATIVES OF DIPHENYL SULPHIDE

NAME	Formula	M.P. °C	Solubility
2,6-Di-iodo-4 amino methoxy Diphenyl sulphide	$C_{13}H_{11}ONSI_2$	172.5	ether
2,6-Di-iodo-4-acetyl amino-4'-methoxy diphenyl sulphide	$C_{15}H_{11}O_2NSI$	230	Sl. alcohol
Hydrochloride of 2, 6-di-iodo-4-amino-4'methoxy diphenyl sulphide	$C_{13}H_{12}ONSClI_2$	Decomp 2o	Alcohol

DERIVATIVES OF DIPHENYL ETHER

2, 6-Di-iodo-4-Nitro 2' methoxy diphenyl ether	$C_{13}H_9O_4NI_2$	149.5	Alcohol
2,6-Di-iodo-4-Nitro-3' methoxy diphenyl ether	$C_{13}H_9O_4NI_2$	139.5	Alcohol
2,6-Di-iodo-4-amino-2'-methoxy diphenyl ether	$C_{13}H_{11}O_2NI_2$	178.5	Benzene
2,6-Di-iodo-4-amino-3'-methoxy diphenyl ether	$C_{15}H_{13}O_3NI_2$	124.5	Sl. Alcohol
2,6-Di-iodo-4-acetylamino 2'methoxy diphenyl ether	$C_{15}H_{13}O_3NI_2$	227.5	Sl. Alcohol
2,6-Di-iodo-4-acetylamino 3'-methoxy diphenyl ether	$C_{15}H_{13}O_3NI_2$	177.5	Ethyl Alcohol

Of all the derivatives of diphenyl-sulphide, para-hydroxy-diphenyl-sulphide has been the most outstanding. This compound was found to possess a germicidal activity equivalent to a phenol coefficient of 115.

Law and Johnson[16] have begun a study of practical methods for synthesizing sulphur-ether-a-amino acid combinations corresponding in structure to the naturally occurring protein acids, phenyl-alanine and tyrosine, and also the analog of the hormone-thyroxine. Law and Johnson have succeeded in introducing aldehyde groups into sulphide-ether constructions. Of the various methods previously employed for introducing the aldehyde group into the aromatic nucleus,[17] the method of Stephen,[18], involving conversion of a nitrile to an imide by reduction, and the latter to an aldehyde by hydrolysis, was the only one considered at all practical for accomplishing the purpose.

There are objections to using oxidation processes where sulphides are involved, because the sulphides represent the lowest valency state of sulphur and all reactions which tend to convert respective sulphides to a sulphoxide or a sulphone must be avoided.

The starting points for the two amino acid syntheses were 4, methyl-4'cyandiphenyl sulphide and 4 ethoxy-4'cyandiphenyl sulphide. They were converted into the corresponding aldehydes by the method used by Stephen[17, 18] and then condensed with hydantoin according to the method of Wheeler.[19] After reducing the aldehyde condensation product, and destroying the resulting hydantoin derivative by hydrolysis, the alpha-amino-acid was easily obtained. Dealkylation 2,2' ethoxy diphenyl sulphide B-alanine by heating with hydrobromic acid gave the sulphur analog of thyroxine.

A group of diphenyl sulphide derivatives and their properties are given in the following table.[20]

NAME	FORMULA	M. P.	Solubility			
			W	AL	Acet	eth
P-Ethoxy-P'aldehyde-diphenyl sulphide	$C_6H_4OC_2H_5SC_6H_4CHO$	83	i	s	sl s	s
P'methyl-P'aldehyde diphenyl sulphide	$CH_3C_6H_4SC_6H_4CHO$	69	i	i	sl s	s
P-methyl-diphenyl sulphide P'-aldal hydantoin	$CH_3C_6H_4CHCCONHCONHS$	239.5	i	sl s	Sl s	i
P-Ethoxy diphenyl sulphide P'-aldal-hydantoin	$C_2H_5OC_6H_4SC_6H_4HCCCONHCONH$	254	i	sl s	s	i
P-Methyl diphenyl-sulphide P'-aldyl hydantoin	$CH_3C_6H_4SC_6H_4HCCCONHCONH$	187.5	i	sl s	s	i
P-Ethoxy-diphenyl sulphide P'-aldyl-hydantoin	$C_2H_4OC_6H_4SC_6H_4HCCCONHCONH$	184.5	i	sl s	s	i
P-methyl-P'diphenyl sulphide B-alanine	$CH_3OC_6H_4SCH_4C_2CH(NH_2)COOH$	Decom. 199	i	i	i	i
P-Ethoxy-P'-diphenyl B-alanine	$C_2H_4SC_6H_4CH_2CH(NH_2)COOH$	Decom. 209	i	i	i	i
P-Hydroxy-P' diphenyl sulphide B-alanine	$HOC_6H_4SC_6H_4CH_2CH(NH_2)COOH$	Decom. 241	i	i	i	i

W --- Water

Al --- Alcohol

Acet --- Acetic Acid

Eth --- Ether

S --- Soluble

I --- Insoluble

Sl. s -- Slightly Soluble

PURPOSE OF THIS WORK

The therapeutic value of the diaryl sulphides has been a subject of much recent investigation. The halogen derivatives, especially iodine, or diphenyl-sulphide, have been carefully studied.

The purpose of this work is not to study the therapeutic value of the diaryl sulphides, but to study some of the methods of preparation, and to determine the physical constants of a few of the compounds. Further, to study the relationship that exists between the diphenyl sulphides and the diphenyl ethers will be a part of this task.

EXPERIMENTAL PART

THIO-PHENOL:

Thio-phenol was prepared in order to insure the purity of the starting material.

100 grams of phenol and 70 grams of phosphorus penta-sulphide were mixed in a 500 cc. Florence flask. The flask was then fitted with a reflux condenser and the contents heated slightly above the boiling point for three hours. The apparatus was then arranged for distillation. An air was found to serve the purpose better than a water condenser. The contents of the flask were heated cautiously. At 159-160°C phenol and water came over. After the unchanged phenol and water had passed over, the temperature rose to 166.5°C. The receiver, of course, was changed when the temperature began to rise in order to receive the product that came over at the higher temperature. The distillate which came over at 165-169°C was a yellow liquid, which was found to be thio-phenol with traces of phenol and water. The compound was washed free of phenol with alcohol and then dried over calcium chloride. It was then redistilled at 169.5°C. The specific gravity of thio-phenol was found to be 1.0778. Its solubility was tested in water, alcohol, ether, and benzene. It was soluble in benzene and ether, partially soluble in alcohol, but insoluble in water.

DIPHENYL SULPHIDE:

50 grams of thio-phenol were refluxed with 45 grams of phenol and 25 grams of phosphorus penta-sulphide for 5 hours at 230° to 245°C.

An investigator reports a preparation in which the temperature was allowed to rise above 250°C. at the beginning of the process. He states this resulted in the formation of a large quantity of diphenyl disulphide, and a large amount of a resinous product.

The apparatus was changed for distillation with an air condenser. The product which came over between a temperature of 290°C and 300°C was collected, washed, free of all traces of phenol with alcohol and dried over calcium chloride. After drying, the product was subjected to distillation again. The pure diphenyl sulphide distilled at 295°C. The temperature was allowed to rise to 297°C and was held at that temperature for 30 minutes. The diphenyl sulphide was found to be insoluble in water, very soluble in ether, and soluble in benzene. The specific gravity was found to be 1.1302, yield, 74.26%.

The product that remained in the flask after distillation solidified upon cooling. The boiling point, melting point, and solubility tests substantiated the belief that the crystalline substance was diphenyl disulphide. It was insoluble in water, soluble in benzene, alcohol, and ether. It melted at about 54°C; the boiling point was 307.5°C.

2, 2' BROMO-DIPHENYL SULPHIDE

50 cc. of diphenyl sulphide, 1 gram of powdered iron and 25 cc. of bromine were mixed in a 250 cc. Florence flask. The bromine was added slowly through a separatory funnel. The cork of the flask contained a delivery tube that terminated in a beaker containing water, and a thermometer. The gas that passed over while the flask was warmed gently for 30 minutes on the water bath dissolved in the water. The product was treated with a dilute solution of sodium

hydroxide. The oily layer was drawn from the alkaline solution by the use of a separatory funnel. It was distilled. The distillate came over at 331.6°C. It was dried over calcium chloride for 10 hours and distilled again. Yield, 59% .

2, 2'-Nitro-Diphenyl-Sulphide:

50 grams of diphenyl sulphide were placed in a 250 cc. Florence flask, and a mixture of 120 cc. of concentrated Nitric Acid and 160 cc. of Glacial Acetic Acid was added slowly through a separatory funnel. Between each addition of the mixture, the flask was shaken vigorously. The temperature of the contents was watched, and the flask was placed under the tap at various intervals to prevent the temperature from rising above 50°C.

When all of the nitrating mixture had been added, the separatory funnel was removed and the contents were refluxed gently on the water bath for three hours. After the contents of the flask were allowed to cool to room temperature, they were poured into a suction funnel. The long colorless needles of 2, 2'-nitro diphenyl sulphide remained in the funnel. These crystals were washed three times with cold water, twice with a dilute solution of sodium carbonate in order to free them of any acid that might have been left unchanged, and washed a second time with cold water. The mother liquor was evaporated and a few more crystals were obtained.

The crystals were then allowed to dry and their properties were tested. The melting point was found to be 38°C. The crystals were insoluble in water and alcohol, but soluble in ether, benzene, and chloroform. Yield was only about 18.3% of the theoretical yield.

2, 6- DI-IODO-4-NITRO-4'-METHOXY DIPHENYL SULPHIDE

Fifty grams(0.1 mole)of 3,4,5, tri-iodo-nitro benzene and fourteen

grams(0.1 mole)of 4-methoxy thio-phenol were added to 250 cc. of boiling methyl ethyl ketone. To this mixture was added thirty grams of finely powdered, anhydrous potassium carbonate. After heating under a reflux condenser and in a current of hydrogen gas for five hours., the mixture was filtered. On cooling the filtrate, the bright yellow crystals of the pure nitro compound were obtained. The yield was increased by evaporating the mother solution and allowing it to cool. It was crystallized from acetone or methyl ethyl ketone. The yield was thirty grams or sixty per cent.

SUMMARY AND CONCLUSIONS

1. The purity of the Nitro derivative of diphenyl sulphide was doubtful.

2. The position of the nitro group was not determined but it is believed that it took the ortho position.

3. The iodine derivatives of diphenyl sulphide were extremely soluble in water; consequently, they did not exhibit any bactericidal activity when tested in the usual way.

4. Preparation of diphenyl sulphide from thio-phenol, phenol, and phosphorus penta-sulphide gives the best yield.

5. The procedure is simple.

6. The Stephen reaction for preparing Aldehydes from cyanides has been applied with success in the diaryl-sulphide series.

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BIOGRAPHY

Andrew Carnegie Lovett was born three miles southwest of Kerens, Texas, March 20, 1907. His elementary school work was done in the rural schools of his birthplace. Two years of his high school work were done at Powell's High School, four miles northwest of the place of his birth. The last two years of his high school work were done in the high school department of Paul Quinn College, Waco, Texas; completing his high school course, June 5, 1925. He entered Paul Quinn College, as a freshman in September, 1925, and completed his freshman work on June 3, 1926. After remaining out of school for two years, he entered Prairie View State College, where he has pursued work in the Arts and Sciences with a major in Chemistry.

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